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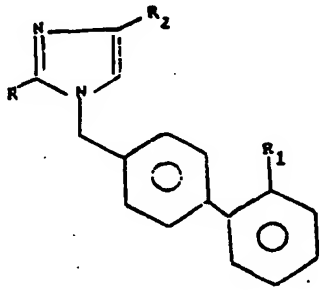
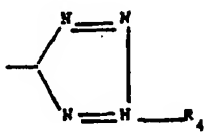
(54) Title: DINITROGENATED HETEROCYCLIC DERIVATIVES HAVING AII-ANTAGONISTIC ACTIVITY

(57) Abstract

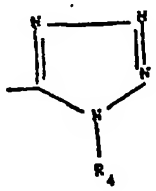
Imidazole derivatives of general formula (I) wherein R is a C_1-C_5 alkyl or a C_2-C_5 alkenyl group; R_1 is a $COOR_3$, CN, $-SO_3H$ group or a tetrazole group of formula (IIa) or (IIb); R_2 is a pyrazine, pyrimidine or pyridazine ring, optionally substituted with one or more C_1-C_5 alkyl groups, carboxy groups or C_1-C_5 alkoxycarbonyl groups or the N-oxides thereof; R_3 is hydrogen, C_1-C_5 alkyl or benzyl; R_4 is hydrogen, C_1-C_5 alkyl or triphenylmethyl and the salts thereof with pharmaceutically acceptable acids or bases with AII-antagonistic activity, a process for the preparation thereof and pharmaceutical compositions containing them as the active principles.



(I)



(IIa)



(IIb)

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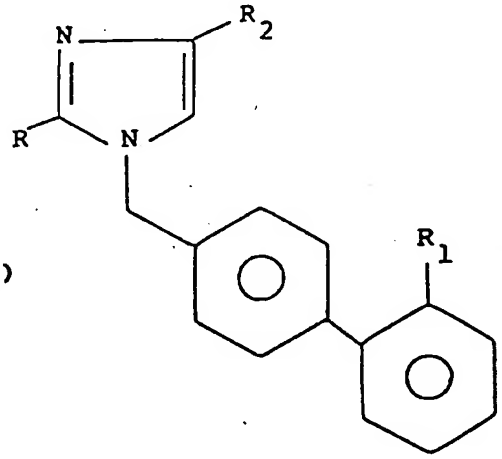
DINITROGENATED HETEROCYCLIC DERIVATIVES HAVING AII-ANTAGONISTIC ACTIVITY

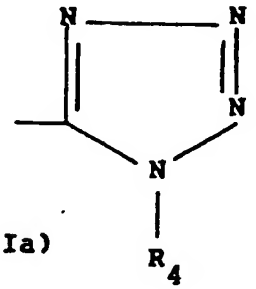
The present invention relates to imidazole derivatives with AII-antagonistic activity, a process for the preparation thereof and pharmaceutical compositions containing them as the active principles.

More particularly, the invention relates to compounds of formula (I)



(I)

wherein R is a C_1-C_5 alkyl or a C_2-C_5 alkenyl group;
R_1 is a $COOR_3$, CN, $-SO_3H$ group or a tetrazole group of formula (IIa) or (IIb)



(IIa)

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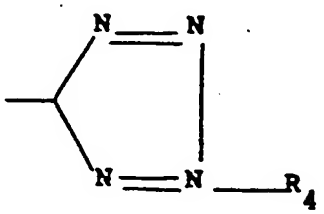


(IIb)

R_2 is a pyrazine, pyrimidine or pyridazine ring, optionally substituted with one or more C_1-C_5 alkyl groups, carboxy groups or C_1-C_5 alkoxycarbonyl groups or the N-oxides thereof;

R_3 is hydrogen, C_1-C_5 alkyl or benzyl;
R_4 is hydrogen, C_1-C_5 alkyl or triphenylmethyl and salts thereof with pharmaceutically acceptable acids or bases.

C_1-C_5 alkyl means straight, branched or cyclic alkyl groups. Examples of said groups comprise methyl, ethyl, n-propyl, cyclopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, isoamyl, cyclopentyl.

Examples of C_2-C_5 alkenyl groups are vinyl, allyl, isoprenyl, 2-butenyl, 3-pentenyl.

Examples of C_1-C_5 alkoxycarbonyl groups comprise methoxycarbonyl, ethoxycarbonyl.

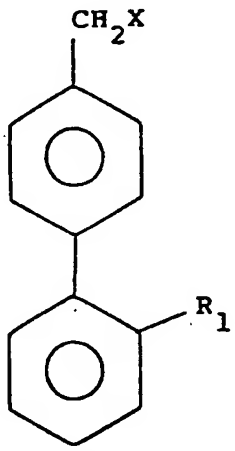
In the compounds of formula (I) R is preferably a C_1-C_5 alkyl group; R_1 is preferably a tetrazole group of formulae (IIa) or (IIb) wherein R_4 is as defined above and preferably hydrogen; R_2 is a 2-pyrimidinyl; 5-pyrimidinyl; 2-methyl-4-methoxycarbonyl-5-pyrimidinyl; 1-oxide-5-pyrimidinyl; 1-oxide-2-pyrimidinyl; 2-pyrazinyl; 2-pyrazinyl-4-oxide; 3-methoxycarbonyl-2-pyrazinyl; 3,6-dimethyl-2-pyrazinyl; 3-pyridazinyl; 3-methyl-6-pyridazinyl; 6-methoxycarbonyl-3-pyridazinyl; 2-oxide-3-methyl-6-pyridazinyl; 1-oxide-3-methyl-6-pyridazinyl, 1-oxide-3,6-dimethyl-2-pyrazinyl and 4-oxide-3,6-dimethyl-2-pyrazinyl ring.

Compounds of formula (I) have antagonistic activity on angiotensin II (AII) and therefore are useful in the pharmacological treatment of such cardiovascular diseases as hypertension, cardiac decompensation, intraocular hypertension, glaucoma, hyperaldosteronism, renal diseases, myocardial infarction.

Compounds with AII-antagonistic activity characterized by a totally substituted imidazole ring were described in EP 253310, EP 324377, WO 91/00277, WO 91/00281, WO 91/14367, WO 91/15206 and WO 92/00977.

Compounds of formula (I), on the contrary, are characterized by a 2,4-disubstituted imidazole group in which the substituent at the 4-position is a 6-membered dinitrogenated heterocyclic ring (pyrimidinyl, pyrazinyl or pyridazinyl) and by advantageous medical-toxycological characteristics.

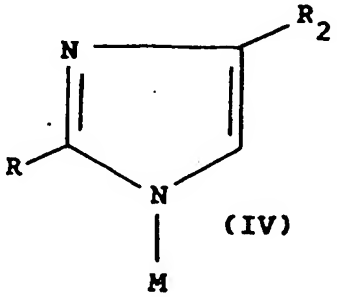
Compounds of formula (I) are prepared by reacting of a compound of formula (III)



(III)

wherein R_1 has the same meanings as R_1 or is a group which can be converted into R_1 by removing the protecting groups and X is a leaving group such as halogen, mesyloxy, acetyloxy

with a compound of formula (IV)

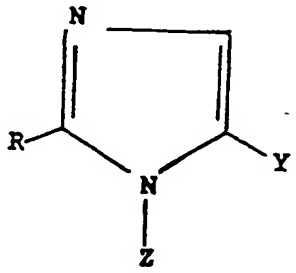


(IV)

wherein R and R_2 are as defined above and M is H, acetyl, p-methoxybenzyl, trityl.

The alkylation reaction can be carried out forming the salt of imidazole (IV), in which M is H, in an aprotic dipolar solvent such as DMF or DMSO by treatment with alkali and alkaline-earth metal (Na, K, Ca) hydrides or alternatively in lower alcohols (MeOH, EtOH, t-BuOH) in the presence of the corresponding Na or K alcoholate at temperatures ranging from 20°C to 100°C.

Compounds of formula (III) can be prepared according to what reported by Carini et al., J. Med. Chem. 34, 2525, 1991, whereas compounds of formula (IV) can be prepared by reacting imidazoles (V), which are in their turn prepared as described by R.M. Keenan et al., J. Med. Chem., 35, 3858 (1992)



(V)

wherein R is as defined above, Y is ZnCl, Bu_3Sn, Me_3Sn, $B(OH)_2$ and Z is a protecting group, with the suitable halogen- pyrimidines, pyridazines or pyrazines. The reaction is carried out in a solvent, such as dioxane, at the reflux temperature, in the presence of transition metal complexes as catalysts, such as palladium complexes, for example palladium tetrakistriphenylphosphine, platinum, nickel (as described for example by M. Peyreyre et al., Tin in organic

synthesis, ButterWorks, London, 1987; R.F. Heck, Palladium reagents in organic chemistry, Academic Press, Orlando, Florida, 1985).

The heteroaryl imidazole compounds (IV), subjected to acidic hydrolysis (both with methanol HCl and with aqueous HCl), to remove the protecting group Z, are subsequently transformed into the corresponding sodium salts by reaction with alkali and alkaline-earth metal (Na, K, Ca) hydrides in aprotic polar (DMF, DMSO), then are reacted with the bromomethyl diphenyl tetrazole derivative (III).

Compounds of formula (I), wherein R_4 is different from hydrogen, finally yield the corresponding compounds (I), wherein R_4 is hydrogen, by heating in methanol in the presence or not of acidic catalysis.

Compounds (I), wherein R_2 is a corresponding N-oxide, can be prepared by oxidation with conventional reagents and subsequent deprotection, again by heating with methanol.

Conventional oxidation reagents are organic or inorganic peracids. Hydrogen peroxide in 20-30% aqueous solution in the presence of variable amounts of glacial acetic acid, or perbenzoic or m-chloroperbenzoic acids in solvents which are preferably dichloromethane or chloroform, at temperatures from 0°C to 60°C, preferably from 0°C to 30°C, can be used.

The compounds of the present invention act as antagonists on AII-receptors. To evaluate the efficacy of the compounds of the invention, <u>in vitro</u> tests (such as the inhibition of the contraction induced by AII in rabbit aorta and the displacement of ^{125}I-Sar^1-Ile^8-AT

II in rat adrenal cortex) and an in vivo test (the inhibition of the pressory response induced by AII in the ganglioblocked normotensive rat) were selected. The compounds of the invention proved active in the above tests; for example in the in vitro test on rabbit aorta, a number of compounds turned out to have pA_2 values higher than 6.5, whereas in the receptor binding they showed to have a Ki <1 μM.

Compounds of general formula (I) or the pharmaceutically acceptable salts thereof can be used in pharmaceutical preparations, alone or in admixture with pharmaceutically acceptable excipients, for the oral or parenteral administrations. Suitable excipients are for example starch, lactose, glucose, arabic gum, stearic acid and the like. The pharmaceutical preparations can be in solid form such as tablets, capsules or suppositories or in liquid form, such as solutions, suspensions or emulsions.

Moreover, if administered parenterally, the pharmaceutical preparations can be in the form of sterile solutions.

Compounds of general formula (I) can be administered in unitary doses ranging from 1 to 100 mg, to patients suffering from cardiac and vascular diseases such as hypertension, acute and chronic cardiac decompensation, intraocular hypertension . However, the use thereof can also be envisaged in other diseases, such as secondary hyperaldosteronism, pulmonary hypertension, renal diseases (glomerulonephritis, diabetic nephropathy) or vascular diseases (hemicrania, Raynaud's disease).

The following examples further illustrate the invention.

EXAMPLE 1

6-methyl-3-[2-butyl-[[2-trimethylsilyl]ethoxy]methyl]-imidazol-5-yl]pyridazine

A mixture of 2-butyl-1-[[2-(trimethylsilyl)ethoxy]methyl]-5-(tributylstannyl)imidazole (6.4 g, 11.86 mmoles) prepared as described in R.M. Keenan et al., J. Med. Chem., 35, 3858 (1992), 3-chloro-6-methylpyridazine (1.52 g, 11.86 mmoles), $Pd(PPh_3)_4$ (0.68 g, 0.59 mmoles), 2,6-di-tert-butyl-4-methylphenol (a spatula tip) in 130 ml of deareated anhydrous dioxane was refluxed for 18 hours under inert atmosphere.

The reaction mixture was added with ethyl ether (180 ml) and 75 ml of a sodium fluoride saturated aqueous solution, then it was stirred at room temperature for 20 hours, was filtered on Celite and the filtrate was washed with a NaCl saturated solution (3 times), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent acetone/$CHCl_3$ = 2/8) to give 2.73 g of pure product (yield = 65%) in the form of a liquid.

Analogously were prepared:

2-[2-butyl-1-[[2-trimethylsilyl]ethoxy]methyl]imidazol-5-yl]pyrimidine;

5-[2-butyl-1-[[2-trimethylsilyl]ethoxy]methyl]imidazol-5-yl]pyrimidine;

2-methyl-4-ethoxycarbonyl-5-[2-butyl-1-[[2-trimethylsilyl]ethoxy]methyl]imidazol-5-yl]pyrimidine;

2-[2-butyl-1-[[2-trimethylsilyl]ethoxy]methyl]imidazol-

5-yl]pyrazine;

3,6-dimethyl-2-[2-butyl-1-[[2-trimethylsilyl]ethoxy]methyl]imidazol-5-yl]pyrazine;

3-methoxycarbonyl-2-[2-butyl-1-[[2-trimethylsilyl]ethoxy]methyl]imidazol-5-yl]pyrazine.

EXAMPLE 2

6-methyl-3-[2-butylimidazol-5-yl]pyridazine

A solution of 6-methyl-3-[2-butyl-1-[[2-trimethylsilyl]ethoxy]methyl]imidazol-5-yl]pyridazine (2.69 g, 7.76 mmoles), 5N HCl (38 ml) was heated to 40-50°C for 3 hours, then alkalinized with concentrated NaOH and extracted repeatedly with chloroform. The combined extracts were washed with a NaCl saturated solution, dried over $MgSO_4$ and evaporated under reduced pressure. The resinous orange residue (1.66 g, quantitative yield) was used as such as in the subsequent reaction.

Analogously were prepared:

2-[2-butylimidazol-5-yl]pyrimidine;

5-[2-butylimidazol-5-yl]pyrimidine;

2-methyl-4-ethoxycarbonyl-5-[2-butylimidazol-5-yl]pyrimidine;

2-[2-butylimidazol-5-yl]pyrazine;

3,6-dimethyl-2-[2-butylimidazol-5-yl]pyrazine;

3-methoxycarbonyl-2-[2-butylimidazol-5-yl]pyrazine;

EXAMPLE 3

2-butyl-4-[6-methylpyridazin-3-yl]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole

A solution of 6-methyl-3-[2-butylimidazol-5-yl]pyridazine (0.84 g, 3.87 mmoles) in anhydrous DMF (40 ml) was added under inert atmosphere with NaH (93 mg, 3.87 mmoles) and the resulting suspension was stirred at

room temperature for 30 minutes, then a solution of N-(triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole 5 (2.16 g, 3.87 mmoles) in DMF (35 ml) was slowly dropped.

The reaction mixture was stirred always at room temperature overnight, then was added with 180 ml of water and ice and repeatedly extracted with ethyl acetate. The combined organic extracts were washed with a NaCl saturated solution, dried over $MgSO_4$ and evaporated under reduced pressure.

The residue was taken up with ethyl ether and filtered, to obtain 2.3 g of a pure product in the form of an orange crystalline solid: m.p. = 163-166°C (Kofler).

Analogously were prepared:

2-butyl-4-[pyrimidin-2-yl]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[pyrimidin-5-yl]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[2-methyl-4-(methoxycarbonyl)-pyrimidin-5-yl]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[pyrazin-2-yl]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[3,6-dimethylpyrazin-2-yl]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[3-(methoxycarbonyl)pyrazin-2-yl]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole.

EXAMPLE 4

2-butyl-4-[6-methylpyridazin-3-yl-1-oxide]-1-[[2'-[1-

triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole and 2-butyl-4-[6-methylpyridazin-3-yl-2-oxide]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole

A solution of 2-butyl-4-[6-methylpyridazin-3-yl]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole (1.35 g, 1.95 mmoles) in 45 ml of CH_2Cl_2, cooled to 10°C, was slowly added with a solution of m-chloroperbenzoic acid (0.345 g, 2.0 mmoles) in CH_2Cl_2, drop by drop. The reaction mixture was stirred at room temperature for 1 hour, then washed with a $NaHCO_3$ saturated aqueous solution (2 x 75 ml) and with water. After drying over $MgSO_4$ and evaporating under reduced pressure, the residue was purified by flash chromatography on silica gel (eluent mixture $CHCl_3$/acetone = 4/1) to obtain 430 mg (31% yield) of 2-butyl-4-[6-methylpyridazin-3-yl-1-oxide]-1-[[2'[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole and 370 mg (27% yield) of 2-butyl-4-[6-methylpyridazin-3-yl-2-oxide]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole.

Analogously were prepared:

2-butyl-4-[pyrimidin-2-yl-1-N-oxide]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[pyrimidin-5-yl-1-N-oxide]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[pyrazin-2-yl-4-N-oxide]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[3,6-dimethylpyrazin-2-yl-1-N-oxide]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]-imidazole;

2-butyl-4-[3,6-dimethylpyrazin-2-yl-4-N-oxide]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]-imidazole;

2-butyl-4-[6-methylpyridazin-3-yl-1-oxide]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[6-methylpyridazin-3-yl-2-oxide]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole.

EXAMPLE 5

2-butyl-4-[6-methylpyridazin-3-yl]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole

A solution of 2-butyl-4-[6-methylpyridazin-3-yl]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]-methyl]imidazole (0.45 g, 0.65 mmoles) in 30 ml of methanol was refluxed for 16 hours, then was evaporated to dryness and the residue was purified by flash chromatography on silica gel (eluent $CHCl_3/CH_3OH$ = 2/1) to obtain 160 mg of a solid: m.p. = 196-199°C (Kofler), ^{1}H-NMR ($CDCl_3$+DMSO): 0.84 (t, 3H), 1.3 (sext, 2H), 1.60 (m, 2H), 2.44 (s, 3H), 2.61 (t, 2H), 4.87 (s, 2H), 6.8 (d, 2H), 6.93 (d, 2H), 7.15-7.45 (m, 4H), 7.59 (s, 1H), 7.66 (d, 1H), 7.94 (d, 1H).

Analogously were prepared:

2-butyl-4-[pyrimidin-2-yl]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole; white solid, m.p. = 141-144°C, ^{1}H-NMR ($CDCl_3$): 0.87 (t, 3H), 1.35 (sext, 2H), 1.62 (quint, 2H), 2.50 (t, 2H), 5.00 (s, 2H), 6.85-7.05 (m, 5H), 7.28 (m, 1H), 7.49 (m, 3H), 7.92 (m, 1H), 8.40 (d, 1H);

2-butyl-4-[pyrimidin-5-yl]-1-[[2'-[1H-tetrazol-5-yl]bi-

phenyl-4-yl]methyl]imidazole; straw-yellow solid, m.p. = 117-118°C, ^{1}H-NMR (DMSO-d_6): 0.84 (t, 3H), 1.31 (sext, 2H), 1.58 (quint, 2H), 2.65 (t, 2H), 5.25 (s, 2H), 7.13 (d app., 4H), 7.5-7.7 (m, 4H), 7.90 (s, 1H), 8.98 (s, 1H), 9.09 (s, 2H);

2-butyl-4-[2-methyl-4-(methoxycarbonyl)-pyrimidin-5-yl]-1-[[2'[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole; solid, m.p. = 125-126°C, ^{1}H-NMR (DMSO-d_6): 0.83 (t, 2H), 1.25 (sext, 2H), 1.55 (quint, 2H), 2.52 (t, 2H), 2.61 (s, 3H), 3.81 (s, 3H), 5.21 (s, 2H), 7.10 (s app., 4H), 7.5-7.71 (m, 5H), 9.11 (s, 1H);

2-butyl-4-[pyrazin-2-yl]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole; ivory-coloured solid, m.p. = 117-120°C; ^{1}H-NMR ($CDCl_3$+DMSO): 0.92 (t, 3H), 1.40 (sext, 2H), 1.69 (quint, 2H), 2.70 (t, 2H), 5.13 (s, 2H), 7.1 (d app., 4H), 7.4-7.7 (m, 5H), 8.34 (d, 1H), 8.41 (d, 1H), 9.1 (s, 1H);

2-butyl-4-[3,6-dimethylpyrazin-2-yl]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole; light brown solid, m.p. = 118-121°C, ^{1}H-NMR ($CDCl_3$): 0.85 (t, 3H), 1.31 (sext, 2H), 1.61 (quint, 2H), 2.36 (s, 3H), 2.55 (t, 2H), 2.66 (s, 3H), 5.04 (s, 2H), 6.86 (d, 2H), 6.95 (d, 2H), 7.24-7.55 (m, 4H), 7.73 (d, 1H), 8.07 (s, 1H);

2-butyl-4-[3-(methoxycarbonyl)pyrazin-2-yl]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole; solid, m.p. = 121-123°C, ^{1}H-NMR (DMSO-d_6): 0.83 (t, 3H), 1.25 (sext, 2H), 1.51 (quint, 2H), 2.66 (t, 2H), 3.84 (s, 3H), 5.31 (s, 2H), 7.1-7.35 (m, 4H), 7.45-7.7 (m, 4H), 7.97 (s, 1H). 8,51 (d, 1H) 8.72 (d, 1H);

2-butyl-4-[pyrimidin-2-yl-1-N-oxide]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole; ivory-coloured

solid, m.p. = 237-243°C, ^{1}H-NMR ($CDCl_3$): 0.90 (t, 3H), 1.38 (sext, 2H), 1.69 (quint, 2H), 2.69 (t, 2H), 5.08 (s, 2H), 6.9-7.13 (m, 5H), 7.35-7.6 (m, 3H), 7.95 (m, 1H), 8.21 (m, 1H), 8.40 (m, 2H);

2-butyl-4-[pyrimidin-5-yl-1-N-oxide]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole; straw-yellow solid, m.p. = 112°C, ^{1}H-NMR (CD_3OD): 0.90 (t, 3H), 1.38 (sext, 2H), 1.59 (quint, 2H), 2.70 (t, 2H), 5.25 (s, 2H), 7.1-7.7 (m, 8H), 7.80 (s, 1H), 8.78 (s, 1H), 8.89 (s, 2H);

2-butyl-4-[pyrazin-2-yl-4-N-oxide]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole; ^{1}H-NMR ($CDCl_3$ + DMSO): 0.94 (t, 3H), 1.43 (sext, 2H), 1.72 (quint, 2H), 2.75 (t, 2H), 5.20 (s, 2H), 7.05-7.5 (m, 9H), 8.4-8.5 (m, 2H), 9.4 (s, 1H).

2-butyl-4-[3,6-dimethylpyrazin-2-yl-1-N-oxide]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole; pink solid, m.p. 109-113°C, ^{1}H-NMR ($CDCl_3$): 0.95 (t, 3H), 1.44 (sext, 2H), 1.77 (quint, 2H), 2.43 (s, 3H), 2.70 (t, 2H), 2.90 (s, 3H), 5.03 (s, 2H), 7.03 (s, app., 4H), 7.25-7.60 (m, 4H), 7.93 (m, 2H), 8.16 (s, 1H);

2-butyl-4-[3,6-dimethylpyrazin-2-yl-4-N-oxide]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole; pink solid, m.p. = 208-212°C, ^{1}H-NMR (CD_3OD): 0.91 (t, 3H), 1.38 (sext, 2H), 1.69 (quint, 2H), 2.47 (s, 3H), 2.69 (t, 2H), 2.76 (s, 3H), 5.09 (s, 2H), 7.0 (d, 2H), 7.14 (d, 2H), 7.39-7.65 (m, 6H), 7.98 (s, 1H);

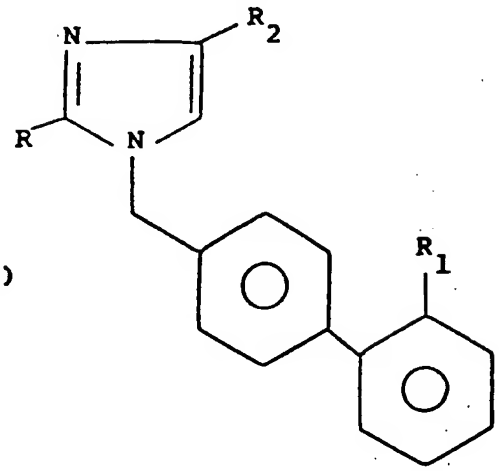
2-butyl-4-[6-methylpyridazin-3-yl-1-oxide]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole; crystalline solid, m.p. = 227-229°C, ^{1}H-NMR ($CDCl_3$+DMSO): 0.92 (t, 3H), 1.40 (sext, 2H), 1.70 (quint, 2H), 2.46 (s,

3H), 2.69 (t, 2H), 5.15 (s, 2H), 7.12 (s app., 4H), 7.48-7.68 (m, 7H);

2-butyl-4-[6-methylpyridazin-3-yl-2-oxide]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole; yellow-whitish crystalline solid, m.p. 133-135°C, ^{1}H-NMR ($CDCl_3$): 0.89 (t, 3H), 1.35 (sext, 2H), 1.65 (quint, 2H), 2.44 (s, 3H), 2.64 (t, 2H), 5.04 (s, 2H), 7.01 (m, 5H), 7.3-7.6 (m, 4H), 7.8 (d, 1H), 8.15 (s, 1H), 8.48 (d, 1H).

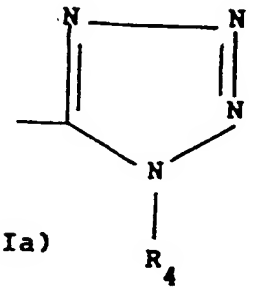
CLAIMS

1. Compounds of general formula (I)



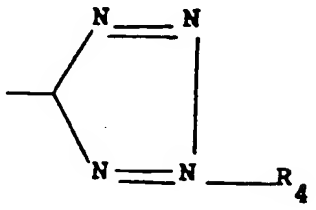
(I)

wherein R is a C_1-C_5 alkyl or a C_2-C_5 alkenyl group;
R_1 is a $COOR_3$, CN, $-SO_3H$ group or a tetrazole group of formula (IIa) or (IIb)



(IIa)

;



(IIb)

R_2 is a pyrazine, pyrimidine or pyridazine ring, optionally substituted with one or more C_1-C_5 alkyl groups, carboxy groups or C_1-C_5 alkoxycarbonyl groups or the N-oxides thereof;
R_3 is hydrogen, C_1-C_5 alkyl or benzyl;
R_4 is hydrogen, C_1-C_5 alkyl or triphenylmethyl and the salts thereof with pharmaceutically acceptable acids or bases.

2. Compounds according to claim 1 wherein R is a C_1-C_5 alkyl group; R_1 is a tetrazole group of formulae

(IIa) or (IIb) wherein R_4 is as defined above and preferably hydrogen; R_2 is a 2-pyrimidinyl; 5-pyrimidinyl; 2-methyl-4-methoxycarbonyl-5-pyrimidinyl; 1-oxide-5-pyrimidinyl; 1-oxide-2-pyrimidinyl; 2-pyrazinyl; 2-pyrazinil-4-oxide; 3-methoxycarbonyl-2-pyrazinyl; 3,6-dimethyl-2-pyrazinyl; 3-pyridazinyl; 3-methyl-6-pyridazinyl; 6-methoxycarbonyl-3-pyridazinyl; 2-oxide-3-methyl-6-pyridazinyl; 1-oxide-3-methyl-6-pyridazinyl, 1-oxide-3,6-dimethyl-2-pyrazinyl and 4-oxide-3,6-dimethyl-2-pyrazinyl ring.

3. A compound according to claims 1-2 selected from the group consisting of:

2-butyl-4-[6-methylpyridazin-3-yl]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[pyrimidin-2-yl]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[pyrimidin-5-yl]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[2-methyl-4-(methoxycarbonyl)-pyrimidin-5-yl]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[pyrazin-2-yl]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[3,6-dimethylpyrazin-2-yl]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[3-(methoxycarbonyl)pyrazin-2-yl]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[6-methylpyridazin-3-yl-1-oxide]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[6-methylpyridazin-3-yl-2-oxide]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;
2-butyl-4-[pyrimidin-2-yl-1-N-oxide]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;
2-butyl-4-[pyrimidin-5-yl-1-N-oxide]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;
2-butyl-4-[pyrazin-2-yl-4-N-oxide]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;
2-butyl-4-[3,6-dimethylpyrazin-2-yl-1-N-oxide]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]-imidazole;
2-butyl-4-[3,6-dimethylpyrazin-2-yl-4-N-oxide]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]-imidazole;
2-butyl-4-[6-methylpyridazin-3-yl-1-oxide]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;
2-butyl-4-[6-methylpyridazin-3-yl-2-oxide]-1-[[2'-[1-triphenylmethyltetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;
2-butyl-4-[6-methylpyridazin-3-yl]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;
2-butyl-4-[pyrimidin-2-yl]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;
2-butyl-4-[pyrimidin-5-yl]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;
2-butyl-4-[2-methyl-4-(methoxycarbonyl)-pyrimidin-5-yl]-1-[[2'[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;
2-butyl-4-[pyrazin-2-yl]-1-[[2'-[1H-tetrazol-5-yl]bi-

phenyl-4-yl]methyl]imidazole;

2-butyl-4-[3,6-dimethylpyrazin-2-yl]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[3-(methoxycarbonyl)pyrazin-2-yl]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[pyrimidin-2-yl-1-N-oxide]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[pyrimidin-5-yl-1-N-oxide]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[pyrazin-2-yl-4-N-oxide]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

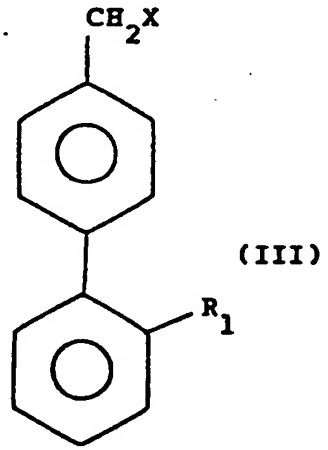
2-butyl-4-[3,6-dimethylpyrazin-2-yl-1-N-oxide]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[3,6-dimethylpyrazin-2-yl-4-N-oxide]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[6-methylpyridazin-3-yl-1-oxide]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole;

2-butyl-4-[6-methylpyridazin-3-yl-2-oxide]-1-[[2'-[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole.

4. A process for the preparation of the compounds of claims 1-3 which comprises reacting a compound of formula (III)

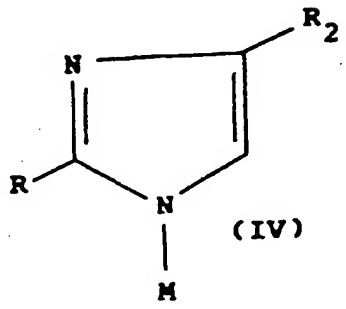


(III)

wherein R_1 has the same meanings as R_1 or a group

convertible into R_1 by removing the protecting groups and X is a leaving group such as halogen, mesyloxy, acetyloxy,

with a compound of formula (IV)



(IV)

wherein R and R_2 are as defined above and M is H, acetyl, p-methoxybenzyl, trityl.

5. The use of the compounds of claims 1-3 as therapeutical agents.

6. The use of the compounds of claims 1-3 as agents having AII-antagonistic activity.

7. The use of the compounds of claims 1-3 for the preparation of a medicament useful in the treatment of cardiac, vascular o renal diseases.

8. Pharmaceutical compositions containing an effective amount of one or more compounds of claims 1-7 as the active ingredient in combination with suitable carriers and excipients.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 95/00468

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D403/14 A61K31/415 A61K31/495 A61K31/50 A61K31/505
//(C07D403/14,257:00,237:00,233:00),(C07D403/14,257:00,239:00,233:00),(C07D403/14,257:00,241:00,233:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,94 03449 (ISTITUTO LUSO FARMACO DITALIA S.P.A.) 17 February 1994 see page 34 - page 39; claims 1,2,6-12	1-8
Y	WO,A,91 00277 (E.I. DU PONT DE NEMOURS AND COMPANY) 10 January 1991 cited in the application see page 177 - page 184; claim 1 see page 137 - page 138; examples 62-67 see page 1, line 20 - line 23	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 May 1995	06. 06. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Fink, D

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INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/EP 95/00468

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		EP-A-	0654030	24-05-95
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		AU-A-	5957990	17-01-91
		CA-A-	2060656	31-12-90
		EP-A-	0479903	15-04-92
		JP-T-	4506522	12-11-92
		US-A-	5354867	11-10-94
		US-A-	5210079	11-05-93